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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Katharina Jacob & Achim Stolle (2014) Microwave-Assisted Azide-Alkyne Cycloaddition in Water Using a Heterogeneous Cu-Catalyst, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:9, 1251-1257, DOI: 10.1080/00397911.2013.850511

To link to this article: http://dx.doi.org/10.1080/00397911.2013.850511

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MICROWAVE-ASSISTED AZIDE-ALKYNE CYCLOADDITION IN WATER USING A HETEROGENEOUS Cu-CATALYST

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GRAPHICAL ABSTRACT



Abstract Several triazoles have been synthesized. They were obtained by a Cu-catalyzed cycloaddition of azides and alkynes. The reaction takes place in aqueous media under microwave irradiation using a copper catalyst based on porous glass. The products have been characterized by infrared, gas chromatography–mass spectrometry, ¹H NMR, and ¹³C NMR in addition to melting = point determination. Furthermore the in situ building of some azides and alkynes and the influence of the used metal species was investigated.

Keywords Alkyne; azide; copper; heterogeneous catalysis; microwave

INTRODUCTION

Huisgen described the reaction of azides and alkynes under thermal conditions forming two triazoles, the 1,4- and the 1,5-substituted regioisomers.^[1] If a copper catalyst is used in this reaction the 1,4-adduct is formed selectively,^[2] whereas the utilization of ruthenium as catalytic metal in respective complexes or salts leads to the 1,5-substituted 1,2,3-triazole.^[3] The mechanistic considerations of both reactions are quite different. With copper, a Cu-acetylide and afterward a six-membered copper(III) metallacycle are proposed as important intermediates. The ruthenium catalyst forms an activated complex with the educts, whereby terminal and internal alkynes can be converted.^[3,4] Most of the known synthetic routes

Received July 12, 2013.

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are carried out with homogeneous catalysts.^[5] In the case of heterogeneous catalysis, only some examples have been reported: Cu/activated carbon,^[6] CuI-polymer catalysts,^[7] Cu/zeolites,^[8] magnetically recoverable CuFe₂O₄,^[9] CuI immobilized on surface-modified silica,^[10] Cu/chitosan,^[11] ionic liquid-Cu(I) complex,^[12] and Cu/porous glass, to name a few.^[13] The application of Cu-nanoparticles has been described also,^[6c,14] whereas in Ru-catalyzed reactions only homogeneous variants have been reported.^[5c,15] It was possible to evaluate the general applicability of a solid Cu/porous glass catalyst by performing copper-catalyzed azide-alkyne cycloaddition reactions with different substrates. Beside terminal alkynes some internal alkynes were assessed also. The products were characterized by infrared (IR) measurement, ${}^{1}H$ - and ${}^{13}C$ NMR, as and by their melting points, in cases of solid products. Furthermore, catalysts with different metals are used to investigate the influence of the active species on the selectivity of the reaction. In addition to Cu-based catalysts, porous glasses coated with Ru or transition metals such us rhodium, palladium, cobalt and silver were compared with respect to their activity and reactivity.

RESULTS AND DISCUSSION

The catalyst used for the present investigations is porous glass, which is practically a quartz glass with defined pore structure.^[16] The aspherical glass particles were impregnated with $Cu(OAc)_2$ and calcined for a specific amount of time to avoid leaching of the metal from the support material. The catalyst was characterized using ICP-OES, BET, and microscopic studies to gain information on the actual metal loading, surface area, and metal particle dispersion on the support's surface.^[13] This catalyst was subjected to catalytic tests in a laboratory microwave reactor. The reaction of benzyl azide (1a) or azidodecane (1b) and alkynes (2) forming 1,2,3-triazoles (3; Scheme 1) was investigated using water as solvent and sodium ascorbate as reducing agent.

The application of different metal precursors in the catalyst preparation resulted in different porous glass catalysts (metal/TP), which were subjected to the model reaction (1a and phenylacetylene, 2a; Fig. 1). All catalysts have the same metal loading of 1 wt% and were used after calcination. The copper-containing catalysts reach selectivities for the 1,4-substituted 1,2,3-triazole of >98%. The other metal precursors did not influence the selectivity and conversion, which is especially evident when compared to the blank test, which is identical to the thermal cycloaddition process. The conversion is always below 15%, mostly 10%. The catalysts deliver a mixture of both triazole isomers in a 1:1 ratio, even for the Ru/TP catalyst. Moreover, utilization of Ru/TP in dimethylformamide (DMF) as solvent as indicated in the literature for homogeneous catalysis^[17] did not give any conversion under the present experimental conditions. Only the application of silver (Ag/TP) as catalytic species resulted in approximately 60% selectivity for the 1.4-adduct. The selectivities and conversions of the metal-catalyzed reactions (except for Cu) can be justified with a thermal rather than a catalytic reaction pathway. In the classical Huisgen cycloaddition, the reaction mixture is only heated up without catalysts and both triazole regioisomers are formed in the same proportion.[1,18]



Scheme 1. Copper-catalyzed reaction of azides and alkynes forming 1,4-substituted 1,2,3-triazoles.

Results with the Cu/TP catalyst using different azides and alkynes are summarized in Table 1. Generally, the reactions were regioselective in favor of the 1,4-substituted triazole (>99% selectivity).

The reactions with different alkynes and azides led to accaptable results. The isolated yield for the reaction of 1a and phenylacetylene (2a) is 81% (Table 1, entry 1).



Figure 1. Influence of the metal type on conversion and regioselectivity. (Reaction conditions: 0.5 mmol benzyl azide, 0.55 mmol phenylacetylene, 50 mg catalyst, theoretical metal-loading 1 wt%, 50 mg sodium ascorbate, 5 ml deionized H₂O, microwave heating, 10 min, 80 °C; the conversion was calculated about a calibration with benzyl azide measured with GC-FID; the selectivity was calculated out of the peak area ratio.) *without sodium ascorbate.

Entry	Azide	Alkyne	Triazole	Isolated yield ^a [%]	analytical yield ^b [%]
1	1a	2a	3 a	81	91
2	1a	2b	3b	72	88
3	1a	2c	3c	43	87
4	1a	2d	3d	90	92
5	1a	2e	3e	95	93
6	1a	2f	3f	80	97
7	1a	2 g	3g	90	98
8	1a	2 h	3h	95	96
9	1a	2i	3i	45	80
10	1a	2j	3j	66	58
11^{c}	1a	2k	3i	43	69
12	1a	21	No reaction	_	
13	1a	d + KF	No reaction	_	
14^e	1b	2a	3 m	44	54

Table 1. Results from the Cu/porous glass-catalyzed azide-alkyne cycloaddition (Scheme 1)

Note. Reaction conditions: 0.5 mmol azide (1), 0.55 mmol alkyne (2a), 50 mg catalyst, theoretical Cu-loading 1 wt%, 50 mg sodium ascorbate, 5 ml deionized H₂O, microwave heating, 10 min, 80 °C (300 W). ^{*a*} Isolated yields (averages from two independent reaction sequences).

^b The analytical yield was determined from conversion calculated via calibration with benzyl azide measured with GC-FID.

^c Same product as entry 9.

^d Alkyne = 2-(trimethylsilyl)phenyl trifluoromethanesulfonate.

^e Reaction at 100 °C.

The application of p-tolylacetylene (2b) resulted in 72% yield, whereas the reaction of *p*-methoxyphenylacetylene (2c) and 1a led to inferior yields only. The values for 1-decyne (2d), 1-dodecyne (2e), and 3-methyl-1-penten-4-yn-3-ol (2g) are greater than 90%. Using 2-methyl-3-butyn-2-ol (2f) as the alkyne only 80% isolated product was achieved. The product from dehydrolinalool (2h) and 1a yielded 95% of the respective triazole. Similar to the reaction with 2c, the Cu-catalyzed reaction of 1a with methyl propiolate (2i) or 2k afforded only 45 and 43%, respectively. Conversion of 2k under the experimental conditions afforded a product identical to the one resulting from the reaction of 2i (based on spectroscopic characterization with ¹H and ¹³C NMR as well as retention time in chromatographic studies). The protecting group (TMS) was apparently cleaved in situ, forming the terminal alkyne. Subjecting 2a to the reaction in presence of **1b** gave only 44% isolated yield, whereas the analytical yield is insignificantly higher. The utilization of methyl 4-hydroxy-2-hexynoate (21) as well as the employment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate as alkynes showed no reactivity at all under the experimental prerequisites. The last alkyne is a typical aryne precursor. To remove the protecting groups and initiate the aryne formation, KF was added. Unfortunately, no reaction was observed, which can be justified due to the low basicity of KF in comparison to, for instance, CsF in presence of 18-crown-6.[19]

Different attempts were conducted to carry out S_N 2-substitution and Cu-catalyzed azide–alkyne cycloaddition as a one-pot reaction (Scheme 2, Table 2).^[10a,20] The conversions of **2a**, sodium azide, and *p*-chlorotoluene or 1-chlorodecane gave no reaction at all. Only the use of benzyl chloride was successful resulting in a conversion of >50%. The yield of the final 1,4-substituted 1,2,3-triazole was 23 or 40% depending on the reaction temperature. The regioselectivity was greater than 95% in favor of **3**, whereas the

POROUS GLASS IN CLICK CHEMISTRY

	$2a \xrightarrow{R-CI, NaN_3} \underbrace{[Cu]}_{H_2O, microwave}$	Ph	R-N ₃
Entry	Chloride (R-Cl)	Conversion of R-Cl ^{<i>a,b</i>} [%] at 80/100 °C	Yield for 3 ^{<i>a,c</i>} [%] at 80/100 °C
1 2 3 4	<i>p</i> -Chlorotoluene 1-Chlorodecane Benzyl chloride Benzyl chloride ^d	No reaction No reaction 42/51 49/63	 23/40 37/55

Table 2. One-pot reaction of chlorides, sodium azide, and phenylacetylene (2a

Note. Reaction conditions: 0.5 mmol chloride, 0.5 mmol NaN₃, 0.55 mmol **2a**, 50 mg catalyst, theoretical Cu-loading 1 wt%, 50 mg sodium ascorbate, 5 ml deionized H_2O .

^a Microwave heating, 10 min (300 W).

^b The conversion of chloride was calculated from calibrated peak area of GC-FID.

^c Yield of the azide was calculated from the peak area ratio of the product.

^{*d*} Without sodium ascorbate.

difference between conversion of Bn-Cl and **3** equals the in situ–formed amount of **1a**. In the first step **1a** is formed in situ and afterward the triazole can be synthesized by Cu-catalyzed cycloaddition. By an increase of the reaction time the selectivity can be improved. As side product small amounts of benzyl alcohol (<5%) were formed due to the solvolysis of the chloride. Reaction in the absence of sodium ascorbate seems to confirm the findings of Mohammed *et al.* (clay-supported Cu-catalyst)^[21] that the selectivity can be increased, resulting in greater conversions and yields. Especially the ratio of **3** and **1a** increases in favor of the former, which might be a starting point for further optimization. However, under the present reaction conditions the effect is less pronounced as reported earlier for the evaluation of the role of sodium ascorbate in the Cu/TP-catalyzed cycloaddition of **1a** and **2a** as well as for the solid-state cycloaddition of **1b** and **2a**.^[13,22]

CONCLUSION

The microwave-assisted reaction of alkynes and azides in water using porous glass as catalyst support is widely applicable. Different alkynes and two azides were converted successfully. Most of the reactions yield more than 40% of the product in isolated form. Additionally, it has been demonstrated that some internal alkynes were able to be converted as well as several propargylic alcohols. Likewise, the in-situ reaction of benzyl chloride, sodium azide, and phenylacetylene was realized. The use of different metal species for the catalyst preparation did not show high conversions, as expected.

EXPERIMENTAL

Substrates, catalyst precursors, and methyl-test-butyl ether (MTBE) were purchased from Alfa Aesar, Sigma-Aldrich, or Merck. The porous glass support was purchased from VitraBio (Steinach, Germany). All chemicals were used without further purification.

Standard Preparation Procedure for Catalysis

 $Cu(AcO)_2$ monohydrate (0.16 mmol, 32 mg) was dissolved in 50 ml ethanol in a round-bottom flask. The porous glass support (1 g) was added to the mixture. The suspension was sonicated for 5–10 min at room temperature (ultrasound bath). After the removal of the solvent in vacuum, the catalyst was calcined in air atmosphere for 2h at 300 °C in a muffle furnace (START, MLS GmbH, Leutkirch, Germany). A catalyst with a metal loading of 1 wt% Cu was achieved.

General Reaction Procedure

The synthesized catalyst (50 mg, theoretical Cu loading 1 m%) was weighted in a MonoPrep reaction vessel (PTFE-coated glass tube for microwave applications). Sodium ascorbate (0.25 mmol, 50 mg), alkyne (0.55 mmol), azide (0.5 mmol), and 5 ml deionized water were added. After sealing the tube it was placed in middle of the cavity of a microwave reactor (ETHOSplus, MLS GmbH, Germany), and equipped with a fiber-optic sensor for temperature measurement. The maximum power input was set to 300 W during the reaction and 500 W while heating up (2 min).

After the reaction, the catalyst was separated by filtration. Solid products were washed with water. Afterward the products were dissolved in MTBE. The solvent was removed under vacuum and the triazoles resulted. For liquid products the catalyst was filtered off and washed with MTBE. The aqueous phase was extracted twice with 10 ml MTBE. The concerned organic phases were distillated under vacuum to remove the solvent and educts.

The products were analyzed with NMR after dissolution in an appropriate solvent and measured with IR at room temperature. For solid products, the melting point was determined. Characterization data and spectral data can be found in the Supporting Information to this article.

Analytical Information

For the characterization of the products a Bruker Avance system was used for NMR measurements. The chemicals were dissolved in $CDCl_3$ and surveyed at room temperature. GC-MSD measurements were performed on 6890 N from Agilent Technologies. Conditions for GC-MSD: HP 5, $30m \times 0.32 mm \times 0.25 \mu m$; 10 psi He; injector temperature 280 °C; detector: electron impact (70 eV). Temperature program: 70 °C (hold 3 min), 15 K min⁻¹ up to 280 °C (hold for 8 min). Melting points were determined using the SMP 10 melting-point equipment from Bibby Stuart Scientific. The IR spectrums were recorded with the FT-IR Spectrometer Spectrum 100 from Perkin-Elmer. The substances were placed directly on the analysis section without prior treatment (ATR measurements).

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

REFERENCES

- 1. Huisgen, R. Proc. Chem. Soc. 1961, 357-396.
- Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. Angew. Chem. Int. Ed. 2002, 41, 2596–2599.
- Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. J. Am. Chem. Soc. 2008, 130, 8923–8930.
- (a) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. J. Am. Chem. Soc. 2005, 127, 210–216; (b) Spiteri, C.; Moses, J. E. Angew. Chem. Int. Ed. 2010, 49, 31–33.
- (a) Salmon, A. J.; Williams, M. L.; Maresca, A.; Supuran, C. T.; Poulsen, S. A. *Bioorg. Med. Chem. Lett.* 2011, *21*, 6058–6061; (b) Johansson, J. R.; Lincoln, P.; Nordén, B.; Kann, N. J. Org. Chem. 2011, *76*, 2355–2359; (c) Nulwala, H.; Takizawa, K.; Odukale, A.; Khan, A.; Thibault, R. J.; Taft, B. R.; Lipshutz, B. H.; Hawker, C. J. *Macromol.* 2009, *42*, 6068–6074.
- 6. (a) Fuchs, M.; Goessler, W.; Pilger, C.; Kappe, C. O. Adv. Synth. Catal. 2010, 352, 323–328; (b) Lee, C. T.; Huang, S.; Lipshutz, B. H. Adv. Synth. Catal. 2009, 351, 3139–3142; (c) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. Adv. Synth. Catal. 2010, 352, 3208–3214.
- 7. Chan, T. R.; Fokin, V. V. QSAR Comb. Sci. 2007, 26, 1274-1279.
- Chassing, S.; Sido, A. S. S.; Alix, A.; Kumarraja, M.; Pale, P.; Sommer, J. Chem. Eur. J. 2008, 14, 6713–6721.
- Kumar, A. S.; Reddy, M. A.; Knorn, M.; Reiser, O.; Sreedhar, B. Eur. J. Org. Med. 2013, 4674–4680.
- (a) Miao, T.; Wang, L. Synthesis 2008, 363–368; (b) Shamim, T.; Paul, S. Catal. Lett. 2010, 136, 260–265.
- Martina, K.; Leonhardt, S. E. S.; Ondruschka, B.; Carini, M.; Binello, A.; Cravotto, G. J. Mol. Catal. A: Chem. 2011, 334, 60–64.
- 12. Ahmady, A. Z.; Heidarizadeh, F.; Keshavarz, M. Synth. Commun. 2013, 43, 2100-2109.
- Jacob, K.; Stolle, A.; Ondruschka, B.; Jandt, K. D.; Keller, T. F. Appl. Catal., A 2013, 451, 94–100.
- (a) Raut, D.; Wankhede, K.; Vaidya, V.; Bhilare, S.; Darwatkar, N.; Deorukhkar, A.; Trivedi, G.; Salunkhe, M. *Catal. Commun.* 2009, *10*, 1240–1243; (b) Albadi, J.; Keshavarz, M.; Shirini, F.; Vafaie-nezhad, M. *Catal. Commun.* 2012, *27*, 17–20.
- Lamberti, M.; Fortman, G. C.; Poater, A.; Broggi, J.; Slawin, A. M. Z.; Cavallo, L.; Nolan, S. P. *Organometallics.* 2012, *31*, 756–767.
- 16. Gallert, T.; Stolle, A.; Ondruschka, B. Opt. Appl. 2012, 42, 245-254.
- Liu, P. N.; Li, J.; Su, F. H.; Ju, K. D.; Zhang, L.; Shi, C.; Sung, H. H. Y.; Williams, I. D.; Fokin, V. V.; Lin, Z.; Jia, G. Organometallics. 2012, 31, 4904–4915.
- (a) Michael, A. J. Prakt. Chem. 1893, 48, 94–95; (b) Huisgen, R.; Knorr, R.; Möbius, L.; Szeimies, G. Chem. Ber. 1965, 98, 4014–4021.
- (a) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. Org. Lett. 2008, 10, 2409–2412; (b) Zhang, F.; Moses, J. E. Org. Lett. 2009, 11, 1587–1590.
- (a) Fukuzawa, S. i.; Shimizu, E.; Kikuchi, S. Synlett 2007, 2007, 2436–2438; (b) Savonnet, M.; Bazer-Bachi, D.; Bats, N.; Perez-Pellitero, J.; Jeanneau, E.; Lecocq, V.; Pinel, C.; Farrusseng, D. J. Am. Chem. Soc. 2010, 132, 4518–4519; (c) Fletcher, J. T.; Keeney, M. E.; Walz, S. E. Synthesis 2010, 3339–3345; (d) Mittapelly, N.; Mukkanti, K.; Reguri, B. R. Asian J. Chem. 2013, 25, 483–486.
- Mohammed, S.; Padala, A. K.; Dar, B. A.; Singh, B.; Sreedhar, B.; Vishwakarma, R. A.; Bharate, S. B. *Tetrahedron.* 2012, 68, 8156–8162.
- Thorwirth, R.; Stolle, A.; Ondruschka, B.; Wild, A.; Schubert, U. S. Chem. Commun. 2011, 47, 4370–4372.